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(54) PRODUCTION OF POLYSULFONE HOLLOW FIBER TYPE ARTIFICIAL KIDNEY AND ARTIFICIAL KIDNEY

(57)Abstract:

PROBLEM TO BE SOLVED: To easily produce the artificial kidney having high water permeability and adequate albumin permeability by setting the viscosity and water volume of a stock soln. for spinning contg. a polysulfone resin and hydrophilic high polymer to specific ranges and impregnating the hollow fibers spun from this stock soln. for spinning with a swelling holding material.

SOLUTION: The stock soln. for spinning which has the range from 25 to 130 poises in the viscosity (x) (poise) at 30°C of the stock soln. for spinning contg. the polysulfone resin and the hydrophilic high polymer and has the range satisfying the equation $-0.01x+1.45 \leq y \leq -0.01+2.25$ in the volume (y) (wt.%) of the water included in the stock soln. for spinning is prepd. at the time of producing the hollow fiber type artificial kidney. The hollow fibers spun from the spinning soln. by using an org. solvent, etc., as an injecting liquid are impregnated with the swelling holding material, by which the hollow fibers are formed in the state of sticking the fibers to the aq. soln. of the swelling holding material. In succession, this hollow fiber bundle is

inserted into a module case for the artificial kidney and after the formation of a tube plate is executed, the swelling holding material is washed with water and thereafter, a sterilization treatment is executed.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the artificial kidney used for the hemodialysis and the hemofiltration therapy for the prolongation of life of the patients, such as renal failure, and its manufacture approach.
[0002]
[Description of the Prior Art] The demarcation membrane which consists of polysulfone system resin is widely used with the good mechanical property and thermal resistance.
[0003] Also in the field of an artificial kidney, having the outstanding removal ability of urine poison is explained to JP,5-54373,B, JP,6-238139,A, and JP,4-300636,A.
[0004] However, with the increment in a long-term dialysis patient, a dialysis technique is also diversified and the higher engine performance has come to be required also from an artificial kidney. That is, very high water permeability is required in online filtration dialysis or push pull filtration dialysis, and the high removal ability of the with a molecular weight [, such as beta 2-microglobulin,] of 10,000 or more matter is demanded with the high removal ability of the low-molecular matter in the usual hemodialysis. Moreover, it becomes clear that the harmful matter accumulated in a dialysis patient has joined to albumin together strongly although transparency of the albumin which is the useful protein in blood was a direction pressed down as much as possible until now, the film which makes moderate albumin penetrate is also required, and many improvements of the symptom by the artificial kidney using such film are also reported.
[0005] However, an artificial kidney with which are satisfied of all of these demands is not yet obtained. For example, although the polysulfone film indicated by JP,5-54373,B is good as an artificial kidney, the removal ability of the low-molecular matter in the water permeability or hemodialysis which are required of above-mentioned filtration dialysis is not quite satisfactory. Although the polysulfone film of water permeability shown in JP,4-300636,A is enough, the removal ability of the matter with large molecular weight, such as urea matter, division, and beta 2-microglobulin, is not quite satisfactory. When performing potting under existence of the humid maintenance material (for example, glycerol) given in order to hold water permeability when manufacturing the hollow fiber furthermore obtained as an artificial kidney, there is a big problem on production of it being difficult for potting material, such as polyurethane, to permeate the gap of a hollow filament, and it causing a seal leak by adhesion of a hollow filament comrade.
[0006]
[Problem(s) to be Solved by the Invention] This invention cancels the trouble of the conventional technique, and its water permeability is high and it offers the approach of holding the good property of the film obtained at the time of hollow filament spinning in the artificial kidney with albumin permeability with it, and manufacturing stably and easily. [the high and removal engine performance of urine poison, and] [moderate]

[0007]
[Means for Solving the Problem] The manufacture approach of the polysulfone system hollow filament mold artificial kidney of this invention It is in the range whose viscosity x (poise) in 30 degrees C of the spinning undiluted solution containing polysulfone system resin and a hydrophilic macromolecule is 25-130poise. To and the hollow filament to which spinning of the amount y of the water contained in a spinning undiluted solution (% of the weight) was carried out from the spinning undiluted solution in the range with which are satisfied of a degree type, using the mixed liquor of an organic solvent or an organic solvent, and water as infusion Humid maintenance material is sunk in, after the humid maintenance material water solution has adhered, a hollow filament bundle is created, this hollow filament bundle is inserted in the module case for artificial kidneys, tube plate formation is performed, humid maintenance material is washed with water after creating an intermediate product, and it is characterized by carrying out sterilization processing after that.
[0008]
- The manufacture approach of $0.01x+1.45 <= y <= -0.01x+2.25$ and another polysulfone system hollow filament mold artificial kidney of this invention After it sank humid maintenance material into the hollow filament by which spinning was carried out using the spinning undiluted solution containing polysulfone system resin and a hydrophilic macromolecule and the humid maintenance material water solution has adhered to it The spacer for preventing adhesion of a hollow filament comrade is put in, a hollow filament bundle is created, this hollow filament bundle is inserted in the module case for artificial kidneys, tube plate formation is performed, humid maintenance material is washed with water after creating an intermediate product, and it is characterized by carrying out sterilization processing after that.
[0009] Moreover, the transmission of albumin is 3.0% or less, and the dialysance of the vitamin B12 in the module of 2 is 135 or more 1.3m of film surface products, and the polysulfone system hollow filament mold artificial kidney containing the hydrophilic giant molecule of this invention is characterized by being further filled up with water.
[0010] Moreover, another polysulfone system hollow filament mold artificial kidney of this invention is characterized by for the transmission of albumin being 0.1% or more and 2.4% or less, and the dialysance of the vitamin B12 in the module of 2 being 137 or more 1.3m of film surface products.
[0011]
[Embodiment of the Invention] It holds using the hollow filament which has a property good as an object for artificial kidneys obtained by carrying out spinning under the conditions of the specific dry type section using the specific spinning undiluted solution and infusion which are mentioned later for details, without degrading the property, and considers as an artificial-kidney module. Therefore, after giving the humid maintenance material of sufficient amount for a hollow filament, performing assembly processing of a module and removing humid maintenance material, it considers as a product in the condition of having been filled up with water. Under the present circumstances, if a hollow filament bundle is created where humid maintenance material is given to a hollow filament, since a hollow filament comrade will stick and the tube plate formation by potting material will become difficult, it is a more desirable approach to put in a spacer and to prevent adhesion.
[0012] Namely, where the humid maintenance material of sufficient amount for a hollow filament is given, a hollow filament bundle is created. After performing tube plate formation, the polysulfone system hollow filament mold artificial kidney which washed humid maintenance

material with water, was manufactured by the approach characterized by the appropriate thing [carrying out back sterilization processing], and was obtained It is characterized by for the transmission of albumin being 3.0% or less, and the dialysance of the vitamin B12 in the module of 2 being 135 or more 1.3m of film surface products.

[0013] Furthermore, in this manufacture approach, by adopting desirable conditions given in this application, the artificial kidney characterized by for the transmission of albumin being 0.1% or more and 2.4% or less, and the dialysance of vitamin B12 being 137 or more is obtained, and the artificial kidney characterized by for the transmission of albumin being 0.3% or more and 2.0% or less, and the dialysance of vitamin B12 being 140 or more is obtained in the combination of still more desirable conditions.

[0014] Moreover, in the manufacture approach of this invention, by adopting desirable manufacture conditions, when 191 or more artificial kidneys can obtain, the dialysance of a urea adopts more desirable manufacture conditions, 192 or more artificial kidneys can obtain and the dialysance of a urea adopts still more desirable manufacture conditions, 193 or more artificial kidneys can obtain [the dialysance of a urea].

[0015] Moreover, according to the approach of this invention, when a two or more 500 ml/hr-mmHg-m artificial kidney can obtain and the permeability of the water of a hollow filament adopts more desirable manufacture conditions, the permeability of the water of a hollow filament is possible also for a two or more 600 ml/hr-mmHg-m artificial kidney obtaining. The permeability of the water of a hollow fiber with which the best clinical evaluation result obtained by the approach of this invention was obtained was two or more 800 ml/hr-mmHg-m.

[0016] In order to obtain a good symptom improvement by hemodialysis, 0.6% or more of the permeability (a sieving multiplier is displayed by %) of albumin is desirable, and the upper limit becomes about 2.0 - 3.0% from a limit (4-6g / one therapy) of the amount of protein loss. Namely, the transmission of albumin is 0.6% or more and 2.0% or less, and, as for the desirable mode of this invention, the removal engine performance of low-molecular urine toxin components, such as a urea and a creatine, and macromolecule urine toxin components, such as beta 2-microglobulin, offers a higher artificial kidney compared with elegance conventionally.

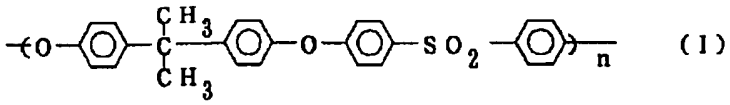
[0017] Although it furthermore has the removal engine performance of high water permeability and a urine toxin component by hemofiltration or hemofiltration dialysis and the permeability of albumin changes with therapy approaches, 0.1% or more and about 1.0% or less are desirable. The permeability of albumin is 1.0% or less, and, as for this invention, the removal engine performance of a urine toxin component and water permeability also offer a higher artificial kidney compared with elegance conventionally.

[0018] In addition, the elimination factor of beta 2-microglobulin and the dialysance of vitamin B12 in clinical evaluation have forward correlation, and the dialysance of vitamin B12 can be called index with the membranous most sufficient engine performance.

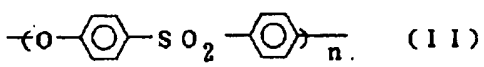
[0019] The polysulfone system hollow filament mold artificial kidney of this invention consists of hollow fibers which consist of polysulfone resin containing a hydrophilic macromolecule.

[0020] What is shown as polysulfone resin by the formula (I) or formula (II) marketed from Amoco Corp., BASF A.G. or ICI, etc. can be illustrated.

[Formula 1]



(I)



(II)

However, n expresses a positive integer among a formula.

[0021] P-3500 or the equivalent device of those of Amoco Corp. which has the structure especially shown by the formula (I) in this is desirable. However, it cannot be overemphasized because of undiluted solution viscosity control that P-1700 etc. is mixable.

[0022] Moreover, although a hydrophilic giant molecule is a giant molecule excellent in hydrophilic properties, such as a polyvinyl pyrrolidone or a polyethylene glycol, especially a polyvinyl pyrrolidone is desirable. The polyvinyl pyrrolidone is marketed from BASF A.G. and GAF, for example, a with a weight average molecular weight [of K-30 or K-90 grade] of 30,000 or more thing is used preferably.

[0023] the annular slit the spinning undiluted solution obtained by the hollow fiber which constitutes the hollow filament mold artificial kidney of this invention dissolving above-mentioned polysulfone resin and an above-mentioned hydrophilic macromolecule in a solvent can carry out the regurgitation of the infusion to a core -- spinning is carried out by discharge and the so-called dryness-and-moisture type spinning method from a mouthpiece.

[0024] independent [in dimethylacetamide, dimethyl sulfoxide, N-methyl pyrrolidone, dimethylformamide, etc.] as a solvent -- or it can be mixed and used. Also in it, dimethylacetamide can obtain the hollow fiber of a property good as an object for artificial kidneys with combination with the water which carries out little addition as the molecular weight and the aperture modifier of a material polymer, and is a desirable solvent.

[0025] the concentration of the polysulfone system resin in the spinning undiluted solution of the manufacture approach of this invention -- desirable -- 14 - 22% of the weight of the range -- it is 17 - 19% of the weight of the range more preferably.

[0026] the concentration of a hydrophilic macromolecule -- desirable -- 5 - 12% of the weight of the range -- it is 7 - 10% of the weight of the range more preferably.

[0027] In order to carry out spinning of the hollow fiber of a property good especially as an artificial kidney at high speed and to obtain it in consideration of economical efficiency, the viscosity of a spinning undiluted solution is important. It becomes [control of the permeability of albumin] difficult and is not desirable while the thread breakage in the dry type section and dispersion of the diameter of a hollow filament become large, when viscosity is low. Moreover, when viscosity is high, while dispersion in the thickness of a hollow filament becomes large, it falls and is not desirable [the removal ability of the urine toxin matter].

[0028] In the spinning undiluted solution of the manufacture approach of this invention, when using dimethylacetamide as a solvent, the viscosity in 30 degrees C has the desirable range of 25-130poise (it sets at 20 degrees C and is about 35-170poise), and its range which is 40-110poise is more desirable.

[0029] Although accommodation of this viscosity can be performed with the concentration of the polysulfone resin in a spinning undiluted solution, molecular weight, the concentration of a hydrophilic macromolecule, and molecular weight, the most desirable approach is changing the molecular weight of a hydrophilic macromolecule. That is, it is the approach of making it into desired viscosity by mixing weight-average-molecular-weight about 40,000 polyvinyl

pyrrolidone (K-30), and molecular-weight about 1,100,000 polyvinyl pyrrolidone (K-90), and, for example, changing the mixing ratio.
[0030] the case where will make polysulfone P-3500 of Amoco Corp. into 18 % of the weight of concentration by using dimethylacetamide as a solvent, and concentration of a polyvinyl pyrrolidone will be made into 9 % of the weight if a desirable example is shown concretely -- the mixing ratio of K-30 and K-90 -- the range of about 9 / 0 - 5/4 -- it becomes the range of about 8 / 1 - 5.5/3.5 more preferably.
[0031] Moreover, in the spinning undiluted solution of this invention, it is desirable to add water little as an aperture modifier of a hollow fiber. when using the dimethylacetamide which is the most desirable solvent, the viscosity of an undiluted solution prescribes the amount y of the desirable water contained in an undiluted solution (% of the weight) -- having -- a degree type -- when it is in the range with which are satisfied of $-0.01x+1.45 \leq y \leq -0.01x+2.25$, the hollow fiber of a good property can be obtained. the amount y of the water contained in an undiluted solution (% of the weight) -- a degree type -- it is more desirable when it is in the range with which are satisfied of $-0.01x+1.65 \leq y \leq -0.01x+2.05$. however, viscosity [in / in x / 30 degrees C of a spinning undiluted solution] (poise) -- it is -- x -- the range of 25-130poise -- it is the range of 40-110poise preferably.
[0032] When there is little addition of water, although generation (generating of the thread breakage in spinning is seen, and comes and is not desirable, if it is expected that polysulfone oligomer crystallizes and becomes cloudy and nebula progresses.) of nebula by the long term storage of a spinning undiluted solution is pressed down, a pole diameter becomes small, and molecular weight, such as beta 2-microglobulin, falls [the removal ability of 10,000 or more matter] and is not desirable [generation]. Conversely, when there is much addition of water, the stability of a spinning undiluted solution becomes poor, nebula-ization takes place, and the permeability of albumin becomes high too much and is not still more desirable.
[0033] Furthermore, in the manufacture approach of this invention, the internal surface of discharge and a hollow filament is controlled for infusion by the freezing characteristic from the core of a mouthpiece, and the film which has a good property as an artificial kidney is obtained. Since it is used the making a spinning undiluted solution solidify slowly from the internal surface of a hollow filament, and making a barrier layer with a precise demarcation membrane form generally as infusion purpose, what has low freezing characteristic is desirable, and mixed liquor with organic solvent independence, such as alcohol, or water is usable.
[0034] Especially, the mixed solution of the solvent and water which are used for a spinning undiluted solution in order to obtain the ease of carrying out of the recovery and the high engine performance at this invention is desirable, and the mixed solvent of the dimethylacetamide and water which are the most desirable solvent is more desirable.
[0035] when using the mixed solvent of this dimethylacetamide and water, in order to obtain the film which has a property good as an artificial kidney of this invention, the amount z of the water contained in infusion (% of the weight) specifies with the viscosity of an undiluted solution -- having -- a degree type -- it is desirable that it is in the range with which are satisfied of $0.14x+25.5 \leq z \leq 0.14x+37.5$. the amount z of the water contained in infusion (% of the weight) -- a degree type -- it is more desirable when it is in the range with which are satisfied of $0.14x+28.5 \leq z \leq 0.14x+34.5$. however, viscosity [in / in x / 30 degrees C of a spinning undiluted solution] (poise) -- it is -- x -- the range of 25-130poise -- it is the range of 40-110poise preferably.
[0036] Furthermore, the film which has a better property as a hollow fiber for artificial kidneys is

obtained when both amount y of the water in an undiluted solution (% of the weight) and amount z of the water in infusion (% of the weight) satisfy each above-mentioned formula.
[0037] Since the coagulation of a spinning undiluted solution is slow and the coagulation from an internal surface is slow when there are few amounts of water, the inclination for the thread breakage in the dry type section to tend to happen, and for the permeability of protein, such as albumin, to become high too much is also seen. Conversely, when there are many amounts of water, if the removal engine performance of the matter with large molecular weight, such as beta 2-microglobulin, falls and the amount of water increases further, it falls and is not desirable [the removal engine performance of the low-molecular matter].
[0038] the spinning undiluted solution and infusion to which the hollow fiber of this invention was set as mentioned above -- using -- an annular slit mold -- the hollow filament from [from a mouthpiece] the wet spinning method led to a direct coagulation bath, or a mouthpiece -- once -- the inside of a gaseous phase -- a pan -- spinning is carried out by the dryness-and-moisture type spinning method drawn behind and into a coagulation bath the bottom. Under the present circumstances, in order to obtain the good engine performance, the dryness-and-moisture type spinning method made to **** in the range for 0.2 - 0.8 seconds more preferably for 0.1 to 1.0 seconds in a gaseous phase (dry type section) is desirable.
[0039] As conditions for the dry type section, 40% or more of relative humidity is required, and the good engine performance can be obtained by making it contact into the humid air current of 70% or more of relative humidity humidified preferably, and making it contact more preferably into the humid air current of 80% or more of relative humidity.
[0040] Next, the undiluted solution of the shape of a hollow filament which did in this way and was spun from the mouthpiece is led to a coagulation bath. In a coagulation bath, although it mixes with a solvent, the coagulation liquid which is the non-solvent which has coagulation ability to polysulfone resin is contacted, and film formation of the rough osculum sponge-like structure as supporters from an outside-surface side is performed.
[0041] Although a non-solvent independent or two sorts or more can be mixed and used as coagulation liquid, the mixed solution of the solvent of the field of recovery of a solvent to a spinning undiluted solution and water is desirable.
[0042] Afterwater washes the hollow filament which came out of the coagulation bath and it removes most solvent components, it is immersed into a humid maintenance material solution, converges on predetermined die length at cutting and a predetermined yarn number, deliquors the humid maintenance material solution with which the infusion inside a hollow filament was permuted at the time of the above-mentioned immersion, and creates a hollow filament bundle.
[0043] Especially a glycerol is desirable, although the alcohols which can prevent desiccation, and the water solution of mineral salt can be used as a humid hold-back agent also when hollow filament bundles, such as a glycerol, ethylene glycol, a polypropylene glycol, and a polyethylene glycol, are left in air.
[0044] In the case of a glycerol, in order to prevent penetrable degradation by desiccation, 65 - 72% of the weight of a glycerol water solution is used still more preferably 60 to 75% of the weight more preferably 50% of the weight or more.
[0045] The coating weight of a humid hold-back agent water solution measures the amount to which this water solution exists in the pore of a hollow fiber, and shows it as ******. Being able to convert this ****** into the membranous rate of pore volume (void content) easily, generally the membranous dialysis engine performance becomes higher [what has higher ******]. In this invention, in order to control [be / it / under / production process / setting] decline in the void

content by desiccation, it manufactures, where high ****** is held and ****** of a hollow fiber offers an artificial kidney with high dialysances, such as a urea and vitamin B12, very highly compared with the conventional polysulfone film.
[0046] namely, ****** of the hollow fiber of the product in the middle of the process which inserts a hollow filament bundle in the module case for artificial kidneys -- 350 - 500% of range -- desirable -- 370 - 460% of range -- it is 390 - 440% of range still more preferably.
[0047] In addition, in order, as for this ******, to fill up with water in many cases in the case of the product, but to abolish the error by the desiccation in the middle of measurement, it permutes by 68% of the weight of the glycerol water solution (specific gravity 1.18), and is measured, and ****** is also computed from that weight. Namely, the weight A of the hollow filament bundle to which the indirect desulfurization liquid of the glycerol water solution enclosed inside the hollow filament was carried out by rotation of 1500rpm in the centrifugal separation machine for 20 minutes, the about 60-90g hollow filament bundle was started, and 68% of the weight of the glycerol water solution adhered After washing the hollow filament bundle with water and removing a glycerol, it is the value which measured the weight B of only the hollow filament dried at 110 degrees C, and was computed by the degree type.
******= (A-B) / Bx100 (%)
In addition, when the spacer is introduced into the surroundings of a hollow filament, measurement of weight A and weight B is performed except for the weight of the spacer.
[0048] Although the fall of the membraneous ability at the time of carrying out assembly processing as an artificial kidney by giving these humid maintenance material can be prevented, conversely, adhesion of a hollow filament comrade takes place, it becomes very difficult in the case of the tube plate formation by potting material, such as polyurethane, to permeate the gap of a hollow filament, and the problem that separation by the tube plate by the side of a lifting, blood, and dialysing fluid cannot perform a seal leak arises. How to keep it in the ambient atmosphere of low humidity as this solution, for a long period of time, after inserting a hollow filament bundle in the case for artificial kidneys For example, beyond about [3 day room] storage), and after applying the air current of low humidity near the both ends of a case very much, a strong vertical air current is further applied to the interior of a room of 40% of relative humidity in the both-ends side of a hollow filament bundle. (-- a thread edge -- rose ****, although there is a method of performing tube plate formation etc. after performing the approach (for example, the perpendicular direction after applying the 40-60-degree C air of 10% or less of relative humidity near the both ends of a case for about 2 hours to air -- strong -- spraying -- the hollow filament of both ends -- rose this morning -- ****) of making it like etc. A more desirable approach is the approach of introducing the spacer for preventing adhesion of a hollow filament comrade the process before creating a hollow filament bundle, after giving humid maintenance material.
[0049] In case the method of introducing this spacer is used as an artificial kidney, dialysing fluid often flows even into the central (core) section of a hollow filament bundle, and the effectiveness of a certain killing two birds with one stone has the effectiveness which raises the dialysis engine performance. installation of this spacer -- one hollow filament or two perimeters -- lines, such as polyester, a polyamide, a polyacrylonitrile, cellulose acetate, silk, and cotton, -- it can add or an object can be performed by the approach of winding spirally so that a hollow filament may be met.
[0050] however -- in order to prevent a seal leak completely by this approach -- a diameter -- the about 1/2 or more (about 120 microns or more)-about thick line of a hollow filament outer

diameter -- it is necessary to use an object, the path of the case of an artificial kidney becomes large, and it is not a not much desirable approach. A more desirable approach is the approach of introducing a spacer into two steps described below. namely, the 1st step -- one hollow filament or two perimeters -- lines, such as polyester, -- the approach of adding an object so that a hollow filament may be met -- A unit hollow fiber component is made with either of the approaches of winding an object spirally. a line -- the perimeter which furthermore gathered these four or more unit hollow fiber components -- the line as the 2nd step of spacers -- it is the approach of winding an object spirally, making a hollow fiber bundle, and making these five or more bundles of hollow fiber bundles the hollow filament bundle which gather and serves as a predetermined hollow filament number for artificial kidneys. In addition, the approach of winding creation of a unit hollow fiber component spirally in this case is a more desirable approach.

[0051] the line introduced into this 1st [the] and the 2nd step -- the crimped staple which an object has a loft comparatively and is elastic, finished yarn, spun yarn, etc. are used preferably. Moreover, it is thin, and the size is to about [of a hollow filament outer diameter] 1/20, and 1/2 to about 1/10 of a hollow filament outer diameter is more desirable than a polysulfone hollow filament.

[0052] By introducing this spacer, where the humid maintenance material of concentration (amount) which can prevent degradation by desiccation of the membranous engine performance is given, tube plate formation becomes easy, this has the removal ability of the high water permeability of this invention, and the high urine toxin matter, and it is obtained with process yield with the high artificial kidney by which the permeability of albumin was controlled to 3% or less.

[0053] Thus, the assembly (modularization) to the artificial kidney of the acquired hollow filament bundle is performed by the usual approach.

[0054] That is, a thread is inserted in the case of polystyrene resin etc., using potting material, such as polyurethane, a centrifugal force is applied, tube plate formation is performed to the both ends of a case, a leakage test is performed, and it considers as the configuration for artificial kidneys.

[0055] Next, a solvent, humid maintenance material, etc. of a minute amount which remain inside a hollow fiber are rinsed and removed, and it sterilizes in the condition of having been filled up with water, and considers as the artificial kidney which is a product. Although the water near a room temperature can also perform this rinsing, in order for 55 degrees C to take the time amount for about 15 minutes at 80 degrees C for about 2 hours, washing by heating water 55 degrees C or more is desirable. Moreover, after washing a short time, repeat washing of performing incubation of 50 degrees C or more, and washing a short time after that is also possible.

[0056] Sterilization can apply sterilization in the condition of having been filled up with the water by the radiation using the sterilization, gamma ray (gamma ray), and electron ray using the usual approach, i.e., hot water 90 degrees C or more. Insolubilization by bridge formation of the hydrophilic macromolecule in the film may take place, and the sterilization by the radiation using a gamma ray or an electron ray is a desirable approach. the case where the most desirable polyvinyl pyrrolidone as a hydrophilic giant molecule is used in this invention -- about 20 -- when a gamma ray is irradiated with the dosage of the range of KGy-35KGy, insolubilization by bridge formation of a polyvinyl pyrrolidone, simultaneously sterilization as a medical device can also be performed to coincidence, and are the most practical sterilization approach.

[0057] Performing insolubilization by bridge formation of a polyvinyl pyrrolidone to

coincidence by this radappertization can press down that elution, and it raises the safety of a product. Moreover, many polyvinyl pyrrolidones in the hollow filament of a product can be made to be able to contain, therefore compatibility with water can serve as good film, and the high engine performance of this application can be made to discover by this approach. In addition, in order to perform insolubilization by bridge formation of a polyvinyl pyrrolidone, it cannot be overemphasized that the approach of carrying out radiation irradiation separately in advance of sterilization is also possible, but the direction which performs bridge formation and sterilization to coincidence by radiation irradiation once is desirable in order to obtain the film of high performance.

[0058]

[Example] Hereafter, this invention is not limited by this although an example explains concretely. Moreover, evaluation of the property of this invention was performed by the following approach.

[0059] Using 30 hollow filaments with a die length of about 15cm which cuts the case of the product artificial kidney which performed [water permeability] gamma ray sterility and was completed, and is obtained, the small glass tube module was created, and the amount of transparency of water was measured by about 100 mmHg(s), and the differential pressure of the inside other than the film, i.e., the differential pressure between film, was expressed with ml/hr-mmHg-m2.

[0060] 60g of [dialysance of urea and vitamin B12] ureas and 1.2g of vitamins B12 were dissolved in 60l. of water, the concentration of the blood side entrance of a dialyzer, an outlet and the inlet port by the side of dialysing fluid, and an outlet was measured by having made amount of blood side streams 200 ml/min, amount of dialysing fluid side streams 500 ml/min, and filtration velocity into 10 ml/min, the dialysance of blood side criteria and dialysing fluid side criteria was computed, respectively, and it displayed by ml/min using the average.

[0061] [Transmission of albumin] hematocrit 30%, protein concentration 6 g/dl and 2l. of 37-degree C bovine blood are put into a beaker, it circulates through amount of blood side streams 200 ml/min, and the differential pressure between film by about 100 mmHg(s) for 1 hour, and the filtrate obtained in the meantime is returned to a beaker. Then, three filtrate was extracted at 15-minute spacing by setting differential pressure between film to about 60 mmHg(s). the albumin concentration in the plasma obtained by carrying out centrifugal separation of the bovine blood -- the BCG method (Wako Pure Chem) -- the albumin concentration in filtrate -- CBB -- it measured by law (Tokyo formation) and albumin permeability was computed from the average value of three filtrate.

[0062] By the six patients of 25 - 35 mg/l, it is 50kg - 60kg in [elimination factor of beta 2-microglobulin] weight, and the beta 2-microglobulin before dialysis amends protein concentration, and computes [with an amounts / of dewatering / 2.5-3.5l. / hemodialysis is performed by using heparin as an anticoagulant in amount of blood side streams 200 ml/min, amount of dialysing fluid side streams 500 ml/min, and 4 hours, the beta 2-microglobulin concentration before and behind dialysis is measured by the latex condensation immunization,], and the average is used.

[0063] Using the [spinning undiluted solution viscosity] Brookfield viscometer (TOKIMEC, INC. DV-BII form digital viscometer), the spinning undiluted solution 300ml or more was extracted and measured so that it might not be influenced of a container bore.

[0064] Example 1 polysulfone The 18 sections (Amoco Corp. make "P-3500") The polyvinyl-pyrrolidone (BASF A.G. make "K-30"; molecular weight 40,000 [about]) 6 section (which

means the "weight section" when only calling it the "section" below), and the polyvinyl-pyrrolidone (BASF A.G. make "K-90"; molecular weight 1,100,000 [about]) 3 section In addition to the mixed solution of the dimethylacetamide 71.95 section and the water 1.05 section, it agitated for 12 hours, and dissolved, keeping it warm at 80 degrees C, and the spinning undiluted solution was prepared. This spinning undiluted solution was the clear liquid which wore opalescence slightly at 30 degrees C according to 76.9poise (it is 113.1poise at 20 degrees C) homogeneity.

[0065] this spinning undiluted solution -- 30 degrees C -- an annular slit -- the infusion which mixed and prepared the dimethylacetamide 60 section and the water 40 section from the core of discharge and a mouthpiece was poured in from the mouthpiece. The die length of a dry type part was set to 250mm, spinning of the moist air of 88% of relative humidity was carried out to the part by spinning rate 40 m/min with the sink, and it led to the 40-degree C coagulation bath (dimethylacetamide/water (weight ratio) = 20/80), and was immersed in the water solution containing 68% of the weight of a glycerol after washing the hollow filament of coagulation bath appearance. After removing the superfluous glycerol adhering to a front face, around two hollow filaments the polyester temporary twist finished yarn of 50-denier five filaments (about 88 microns) Spiral winding was carried out with 0.5 times of number of turns to 10mm of hollow filaments at the Z direction, and it considered as the unit hollow fiber component, and 24 units gathered this unit hollow fiber component, spiral winding of the same polyester finished yarn as the surroundings of it was carried out in the direction of S in the almost same pitch, the spacer was put into two-layer, and the hollow fiber bundle was made. These 221 bundles of hollow fiber bundles were gathered, and the hollow filament bundle was created. This hollow filament bundle was rotated in the centrifugal separation machine, the glycerol water solution which is permuted by the infusion inside a hollow filament and enclosed was deliquored, and it considered as the hollow filament bundle for inserting in the case for artificial kidneys. The bore of this hollow filament is 280 microns in 200 microns and outer diameter, and these hollow filament bundles gathered 10,608 hollow filaments. ****** of this hollow filament bundle was 420%.

[0066] This hollow filament bundle is inserted in the case for artificial kidneys with a bore of 40mm, a temporary cap is attached to both ends, polyurethane was slushed from the dialysing fluid side stream inlet port, and appropriate after polyurethane was solidified at the place of a rotation centrifugal force. Subsequently, the temporary cap was removed, from the both ends of a case, it cut near the edge of the polyurethane and the hollow filament bundle which are disturbed, the header cap was attached, and the leakage test was performed using 0.8kg/cm2 pressurization air.

[0067] Twelve defectives were generated as a result of performing a leakage test using 1000 samples. When the cause was investigated, in case a case is filled up with a hollow filament bundle, it does not originate in the crease yarn by the simple activity mistake by having contacted the edge and wall of a case, and piece yarn, and the seal leak of the polyurethane tube plate section was not seen at all.

[0068] Next, after washing and packing the module which passed the leakage test at 80 degrees C with the pure water which let the reverse osmotic membrane pass for 30 minutes, the gamma ray of 32KGy was irradiated, it sterilized, and the artificial-kidney dialyzer of 2 was created the effective length of 195mm, and the effective area of 1.3m. This dialyzer was what passes dialysis mold hemodialysis apparatus acknowledgement criteria by all items. For the water permeability of the hollow filament started from this module, the transmission of the albumin of 815 ml/hr-mmHg-m2 and a module was [the dialysance of 195 ml/min and vitamin B12 of the dialysance

of a urea] 143 ml/min 1.2%.
[0069] Moreover, the elimination factor of the beta 2-microglobulin at the time of carrying out clinical evaluation using this module is as a result of [very high] 73%, and the point which poses a problem especially on use of residual blood etc. was not seen. In addition, ****** of the hollow filament bundle started from this module was 420%.
[0070] the example 2 polysulfone (Amoco Corp. make "P-3500") 18 section and the polyvinyl-pyrrolidone (BASF A.G. make "K-30") 9 section -- the mixed solution of the dimethylacetamide 71.6 section and the water 1.40 section -- in addition, it agitated for 12 hours, and dissolved, keeping it warm at 90 degrees C, and the spinning undiluted solution was prepared. This spinning undiluted solution was 28.4poise (it is 38.8poise at 20 degrees C) at 30 degrees C.
[0071] this spinning undiluted solution -- 30 degrees C -- an annular slit -- the infusion which mixed and prepared the dimethylacetamide 65 section and the water 35 section from the core of discharge and a mouthpiece was poured in from the mouthpiece. The die length of a dry type part was set to 350mm, spinning was carried out by spinning rate 40 m/min, putting in the part to moist air of 84% of relative humidity, and the artificial-kidney dialyzer was created by the same approach as an example 1 except for the part below. Although 17 defectives were generated as a result of performing a leakage test using 1000 samples by this middle, that cause was the same as the example 1. In addition, ****** of this hollow filament bundle was 380%.
[0072] Thus, the dialyzer of 2 passed dialysis mold hemodialysis apparatus acknowledgement criteria by all items the obtained effective area of 1.3m. The water permeability of the hollow filament started from this dialyzer was 710 ml/hr-mmHg-m2, and the dialysances of a urea and vitamin B12 of modular albumin transmission were 194 ml/min and 139 ml/min 0.4%, respectively. Moreover, the elimination factor of the beta 2-microglobulin at the time of performing clinical evaluation using this module is 67%, and the point which poses a problem especially on use of residual blood etc. was not seen. In addition, ****** of the hollow filament bundle started from this module was 380%.
[0073] the example 3 polysulfone (Amoco Corp. make "P-3500") 18 section and the polyvinyl-pyrrolidone (BASF A.G. make "K-30") 9 section -- the mixed solution of the dimethylacetamide 71.8 section and the water 1.2 section -- in addition, it agitated for 12 hours, and dissolved, keeping it warm at 80 degrees C, and the spinning undiluted solution was prepared. This spinning undiluted solution was 26.8poise at 30 degrees C. The artificial-kidney dialyzer was created by the same approach as an example 1 except having used hereafter the infusion which mixed the infusion presentation with the dimethylacetamide 60 section and the water 40 section. In addition, ****** of a hollow filament bundle used here was 350%.
[0074] The water permeability of the hollow filament started from this dialyzer was 740 ml/hr-mmHg-m2, and the dialysances of a urea and vitamin B12 of modular albumin transmission were 192 ml/min and 136 ml/min 0.1%, respectively. Moreover, the elimination factor of the beta 2-microglobulin at the time of performing clinical evaluation using this module is 62%, and the point which poses a problem especially on use of residual blood etc. was not seen. In addition, ****** of the hollow filament of this dialyzer was 360%.
[0075] 170 bundles reached the gradual hollow fiber bundle, respectively in the middle of example 4 example 1, 306 bundles gathered, the hollow filament bundle was created, the each was inserted in the bore of 35.5mm, and the 46.5mm case for artificial kidneys, and the artificial-kidney dialyzer was produced by the same approach as an example 1.
[0076] 1.0m, when each effective area is 2 1.8m and measured the dialysance of vitamin B12 with 2, it was 127 ml/min and 165 ml/min.

In the middle of example 5 example 3, using the gradual hollow filament bundle, the set number was changed, the hollow filament bundle was made, each was inserted in the case for artificial kidneys (the bore of 35.5mm, 44.0mm, and 46.5mm), and each effective area created the artificial-kidney dialyzer of 2 and 1.8m2 by the same approach as an example 3 1.0m 2 or 1.6m.
[0077] When the dialysance of a urea and vitamin B12 and the permeability of albumin were measured, the dialysance of a urea was [the permeability of 122 ml/min, 147 ml/min and 156 ml/min, and albumin of the dialysance of 187 ml/min, 195 ml/min and 197 ml/min, and vitamin B12] 0.2%, 0.1%, and 0.2%, respectively.
[0078] the example 6 polysulfone (Amoco Corp. make "P-3500") 18 section, the polyvinyl-pyrrolidone (BASF A.G. make "K-30") 6 section, and the polyvinyl-pyrrolidone (BASF A.G. make "K-90") 3 section -- the mixed solution of the dimethylacetamide 71.85 section and the water 1.15 section -- in addition, it agitated for 12 hours, and dissolved, keeping it warm at 90 degrees C, and the spinning undiluted solution was prepared. This spinning undiluted solution was 71.4poise at 30 degrees C.
[0079] this spinning undiluted solution -- 40 degrees C -- an annular slit -- the infusion which mixed and prepared the dimethylacetamide 58 section and the water 42 section from the core of discharge and a mouthpiece was poured in from the mouthpiece. The die length of a dry type part was set to 350mm, moist air of 85% of relative humidity was led to the part by spinning rate 42 m/min with the sink at the 45-degree C coagulation bath, and the artificial-kidney dialyzer was produced by the same approach as an example 1 below. In addition, ****** of the hollow filament bundle in the time of inserting in the gradual case for artificial kidneys the middle was 410%.
[0080] Thus, the water permeability of the hollow filament started from the dialyzer of 2 the obtained effective area of 1.3m was 810 ml/hr-mmHg-m2, and the dialysances of a urea and vitamin B12 of albumin transmission were 195 ml/min and 142 ml/min 0.6%, respectively. Moreover, the elimination factor of the beta 2-microglobulin at the time of performing clinical evaluation using this module is 74%, and the point which poses a problem especially on use of residual blood etc. was not seen. In addition, ****** of the hollow filament of this module was 420%.
[0081] The artificial-kidney dialyzer was produced by the same approach as an example 6 except using the infusion which mixed and adjusted the dimethylacetamide 56 section and the water 44 section using the undiluted solution of example 7 example 6. In addition, ****** of a gradual hollow filament bundle was 400% the middle.
[0082] Thus, the water permeability of the hollow filament started from the dialyzer of 2 the obtained effective area of 1.3m was 760 ml/hr-mmHg-m2, and the dialysances of a urea and vitamin B12 of albumin transmission were 194 ml/min and 140 ml/min 0.2%, respectively. Moreover, the elimination factor of the beta 2-microglobulin at the time of performing clinical evaluation using this module is 71%, and the point which poses a problem especially on use of residual blood etc. was not seen. In addition, ****** of the hollow filament of this module was 410%.
[0083] the example 8 polysulfone (Amoco Corp. make "P-3500") 18 section, the polyvinyl-pyrrolidone (BASF A.G. make "K-30") 7 section, and the polyvinyl-pyrrolidone (BASF A.G. make "K-90") 2 section -- the mixed solution of the dimethylacetamide 71.85 section and the water 1.15 section -- in addition, it agitated for 12 hours, and dissolved, keeping it warm at 90 degrees C, and the spinning undiluted solution was prepared. This spinning undiluted solution was 53.0poise at 30 degrees C.

[0084] this spinning undiluted solution -- 40 degrees C -- an annular slit -- the infusion which mixed and prepared the dimethylacetamide 60 section and the water 40 section from the core of discharge and a mouthpiece was poured in from the mouthpiece, and the artificial-kidney dialyzer was produced by the same approach as an example 6 below. In addition, ****** of a gradual hollow filament bundle was 390% the middle.
[0085] Thus, the water permeability of the hollow filament started from the dialyzer of 2 the obtained effective area of 1.3m was 680 ml/hr-mmHg-m2, and the dialysances of a urea and vitamin B12 of albumin transmission were 193 ml/min and 140 ml/min 0.3%, respectively.
[0086] the example of comparison 1 polysulfone (Amoco Corp. make "P-3500") 18 section, and the polyvinyl-pyrrolidone (BASF A.G. make "K-30") 9 section -- the mixed solution of the dimethylacetamide 44 section, the dimethyl sulfoxide 28 section, and the water 1.0 section -- in addition, it agitated for 15 hours, and dissolved, keeping it warm at 80 degrees C, and the spinning undiluted solution was prepared. This spinning undiluted solution was 32.9poise at 30 degrees C. this spinning undiluted solution -- 30 degrees C -- an annular slit -- the infusion which mixed discharge, and the core of a mouthpiece to the dimethylacetamide 60 section and the water 40 section was poured in from the mouthpiece. Hereafter, the artificial-kidney dialyzer was created by the same approach as an example 1.
[0087] The water permeability of the hollow filament started from this dialyzer was 830 ml/hr-mmHg-m2, and the dialysance of vitamin B12 of modular albumin transmission was 132 ml/min 0.2%. Moreover, the elimination factors of the beta 2-microglobulin at the time of performing clinical evaluation using this module were 49% and a low value. In addition, ****** of the hollow filament of this dialyzer was 340%.
[0088] It was immersed in the water solution containing 45% of the weight of a glycerol after washing the hollow filament of the coagulation bath appearance of example of comparison 2 example 1. After having rolled round to that of six square shapes whose one side is 30cm, or ** after removing the superfluous glycerol adhering to a front face, and carrying out draught drying at a room temperature, it started from **** and the hollow filament bundle was produced. ****** of this hollow filament bundle was 270%. These hollow filament bundles gather 10,608 hollow filaments. A hollow filament bundle is inserted in the case for artificial kidneys with a bore of 40mm, and vertical dry air is applied to the both-ends side of a hollow filament bundle. A thread edge rose this morning After ****, Tube plate formation was performed by the same approach as an example 1, pressurization air was put in from the dialysing fluid side, after performing the leakage test by the bubble point method which fills water to a blood side, gamma ray sterility was performed by the same approach as an example 1, and the artificial-kidney dialyzer was produced.
[0089] In the water permeability of the hollow filament started from this module, 410 ml/hr-mmHg-m2 and albumin transmission became a value with the dialysance of a urea as low [the dialysance of 190 ml/min and vitamin B12] as 125 ml/min 0.3%. That is, in low-concentration glycerol addition, the tube plate formation in those without a spacer was easy, but penetrable degradation of the hollow filament by desiccation took place, and manufacture of the artificial kidney of high engine performance like this invention was difficult. In addition, ****** of the hollow filament of this dialyzer was 300%.
[0090]
[Effect of the Invention] According to this invention, water permeability is high, and the good property of the film obtained at the time of hollow filament spinning in the artificial kidney with albumin permeability with it can be held, and it can manufacture stably and easily. [the high and

removal engine performance of urine poison and] [moderate]

CLAIMS

[Claim(s)]
[Claim 1] It is in the range whose viscosity x (poise) in 30 degrees C of the spinning undiluted solution containing polysulfone system resin and a hydrophilic macromolecule is 25-130poise. To and the hollow filament to which spinning of the amount y of the water contained in a spinning undiluted solution (% of the weight) was carried out from the spinning undiluted solution in the range with which are satisfied of a degree type, using the mixed liquor of an organic solvent or an organic solvent, and water as infusion Sink in humid maintenance material, and after the humid maintenance material water solution has adhered, a hollow filament bundle is created. The manufacture approach of the polysulfone system hollow filament mold artificial kidney characterized by inserting this hollow filament bundle in the module case for artificial kidneys, performing tube plate formation, washing humid maintenance material with water after creating an intermediate product, and carrying out sterilization processing after that.
- $0.01x+1.45 <= y <= -0.01x+2.25$ -- [Claim 2] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 characterized by the amount y (% of the weight) of the water which is in the range whose viscosity x (poise) in 30 degrees C of a spinning undiluted solution is 40-110poise, and is contained in a spinning undiluted solution being in the range with which are satisfied of a degree type.
- $0.01x+1.65 <= y <= -0.01x+2.05$ -- [Claim 3] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 or 2 characterized by the amount z (% of the weight) of the water which is in the range whose viscosity x (poise) in 30 degrees C of a spinning undiluted solution is 25-130poise, and is contained in infusion being in the range with which are satisfied of a degree type.
$0.14x+25.5 <= z <= 0.14x+37.5$ -- [Claim 4] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 or 2 characterized by the amount z (% of the weight) of the water which is in the range whose viscosity x (poise) in 30 degrees C of a spinning undiluted solution is 40-110poise, and is contained in infusion being in the range with which are satisfied of a degree type.
$0.14x+28.5 <= z <= 0.14x+34.5$ -- [Claim 5] The manufacture approach of a polysulfone system hollow filament mold artificial kidney given in any 1 term of claims 1-4 characterized by for a solvent being dimethylacetamide and infusion being a mixed solution of dimethylacetamide and water.
[Claim 6] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 characterized by contacting a hollow filament in the range for 0.1 - 1.0 seconds into the humid air current of 70% or more of relative humidity in the dry type section of a dryness-and-moisture type spinning method.
[Claim 7] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 characterized by contacting a hollow filament in the range for 0.2 - 0.8 seconds into the humid air current of 70% or more of relative humidity in the dry type section of a dryness-and-moisture type spinning method.
[Claim 8] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 characterized by irradiating a gamma ray in the condition of having

been filled up with water, with the dosage of the range of 20 or more KGies and 35 KGies or less, and constructing for it a bridge and insolubilizing a hydrophilic macromolecule after heating water 55 degrees C or more performs washing for removing humid maintenance material.
[Claim 9] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 characterized by putting in the spacer for preventing adhesion of a hollow filament comrade, and creating a hollow filament bundle after the humid maintenance material water solution has adhered.
[Claim 10] After it sank humid maintenance material into the hollow filament by which spinning was carried out using the spinning undiluted solution containing polysulfone system resin and a hydrophilic macromolecule and the humid maintenance material water solution has adhered to it Put in the spacer for preventing adhesion of a hollow filament comrade, and a hollow filament bundle is created. The manufacture approach of the polysulfone system hollow filament mold artificial kidney characterized by inserting this hollow filament bundle in the module case for artificial kidneys, performing tube plate formation, washing humid maintenance material with water after creating an intermediate product, and carrying out sterilization processing after that.
[Claim 11] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 or 10 characterized by sinking in the humid maintenance material of concentration which can prevent penetrable degradation by desiccation to the hollow filament by which spinning was carried out.
[Claim 12] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 11 characterized by for humid maintenance material being a glycerol and the glycerol concentration of the glycerol water solution adhering to a hollow filament being 50 % of the weight or more.
[Claim 13] Introduce an object and a unit hollow fiber component is made. one hollow filament in the condition that the humid maintenance material water solution adhered, or two perimeters -- the line as a spacer -- Wind an object spirally and a hollow fiber bundle is made. the perimeter which gathered these four or more unit hollow fiber components -- the line as the 2nd step of spacers -- The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 or 10 characterized by considering as the hollow filament bundle which gather and inserts these five or more bundles of hollow fiber bundles in the case for artificial kidneys.
[Claim 14] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 or 10 characterized by a hydrophilic giant molecule being a polyvinyl pyrrolidone.
[Claim 15] The polysulfone system hollow filament mold artificial kidney containing the hydrophilic macromolecule which the transmission of albumin is 3.0% or less, and the dialysance of the vitamin B12 in the module of 2 is 135 or more 1.3m of film surface products, and is characterized by being further filled up with water.
[Claim 16] The polysulfone system hollow filament mold artificial kidney characterized by for the transmission of albumin being 0.1% or more and 2.4% or less, and the dialysance of the vitamin B12 in the module of 2 being 137 or more 1.3m of film surface products.
[Claim 17] The polysulfone system hollow filament mold artificial kidney characterized by for the transmission of albumin being 0.3% or more and 2.0% or less, and the dialysance of the vitamin B12 in the module of 2 being 140 or more 1.3m of film surface products.
 [Claim 18] The polysulfone system hollow filament mold artificial kidney according to claim 15

characterized by the dialysance of the urea in the module of 2 being 191 or more 1.3m of film surface products.
[Claim 19] The polysulfone system hollow filament mold artificial kidney according to claim 16 characterized by the dialysance of the urea in the module of 2 being 192 or more 1.3m of film surface products.
[Claim 20] The polysulfone system hollow filament mold artificial kidney according to claim 17 characterized by the dialysance of the urea in the module of 2 being 193 or more 1.3m of film surface products.
[Claim 21] A polysulfone system hollow filament mold artificial kidney given in any 1 term of claims 15-20 characterized by the water permeability of a hollow filament being two or more 500 ml/hr-mmHg-m.
[Claim 22] A polysulfone system hollow filament mold artificial kidney given in any 1 term of claims 15-20 characterized by the water permeability of a hollow filament being two or more 600 ml/hr-mmHg-m.
[Claim 23] A polysulfone system hollow filament mold artificial kidney given in any 1 term of claims 15-20 characterized by the water permeability of a hollow filament being two or more 700 ml/hr-mmHg-m.
[Claim 24] The polysulfone system hollow filament mold artificial kidney according to claim 22 characterized by the elimination factor of the beta 2-microglobulin in clinical use with the hemodialysis mode in the module of 2 being 60% or more 1.3m of film surface products.
[Claim 25] The polysulfone system hollow filament mold artificial kidney according to claim 23 characterized by the elimination factor of the beta 2-microglobulin in clinical use with the hemodialysis mode in the module of 2 being 70% or more 1.3m of film surface products.
[Claim 26] The polysulfone system hollow filament mold artificial kidney according to claim 15 characterized by a hydrophilic giant molecule being a polyvinyl pyrrolidone.
[Claim 27] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 or 10 characterized by ****** of a hollow filament being 350% or more and 500% or less.
[Claim 28] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 or 10 characterized by ****** of a hollow filament being 370% or more and 460% or less.
[Claim 29] The manufacture approach of the polysulfone system hollow filament mold artificial kidney according to claim 1 or 10 characterized by ****** of a hollow filament being 390% or more and 440% or less.
[Claim 30] The polysulfone system hollow filament mold artificial kidney according to claim 15, 16, or 17 characterized by ****** of a hollow filament being 350% or more and 500% or less.
[Claim 31] The polysulfone system hollow filament mold artificial kidney according to claim 15, 16, or 17 characterized by ****** of a hollow filament being 370% or more and 460% or less.
[Claim 32] The polysulfone system hollow filament mold artificial kidney according to claim 15, 16, or 17 characterized by ****** of a hollow filament being 390% or more and 440% or less.

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最終頁に続く

(54)【発明の名称】ポリスルホン系中空糸型人工腎臓の製造方法および人工腎臓

(57)【特許請求の範囲】

【請求項１】

ポリスルホン系樹脂と親水性高分子を含む紡糸原液に、注入液として有機溶剤または有機溶剤と水との混合液を用いて紡糸された中空糸に、湿潤保持材を含浸し、湿潤保持材水溶液が付着した状態で、中空糸束を作成し、該中空糸束を人工腎臓用モジュールケースに挿入し、管板形成を行なって中間製品を作成後、湿潤保持材を水で洗浄し、その後滅菌処理する中空糸型人工腎臓の製造方法において、湿潤保持材を除去するための洗浄を５５℃以上の加熱水で行った後、水を充填した状態で２０ＫＧｙ以上、３５ＫＧｙ以下の範囲の線量でガンマー線を照射し、親水性高分子を架橋して不溶化することを特徴とするポリスルホン系中空糸型人工腎臓の製造方法。

【請求項２】

アルブミンの透過率が０．３％以上、２．０％以下であり、かつ膜面積１．３m^2のモジュールでのビタミンB_{12}のダイアリザンスが１４０以上であることを特徴とするポリスルホン系中空糸型人工腎臓。

【請求項３】

膜面積１．３m^2のモジュールでの血液透析モードでの臨床使用におけるβ_2－ミクログロブリンの除去率が６０％以上であることを特徴とする請求項１または２に記載のポリスルホン系中空糸型人工腎臓。

【請求項４】

膜面積１．３m^2のモジュールでの血液透析モードでの臨床使用におけるβ_2－ミクログ

ロブリンの除去率が７０％以上であることを特徴とする請求項１または２に記載のポリスルホン系中空糸型人工腎臓。

【請求項５】

親水性高分子がポリビニルピロリドンであることを特徴とする請求項１～４のいずれかに記載のポリスルホン系中空糸型人工腎臓。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】

本発明は、腎不全などの患者さんの延命のための血液透析や血液濾過療法に用いられる人工腎臓およびその製造方法に関する。

【０００２】

【従来の技術】

ポリスルホン系樹脂からなる分離膜は、その良好な機械的特性や耐熱性によって広く利用されている。

【０００３】

人工腎臓の分野においても、すぐれた尿毒物質の除去能を有することが、特公平５－５４３７３号公報，特開平６－２３８１３９号公報，特開平４－３００６３６号公報に説明されている。

【０００４】

しかしながら、長期透析患者の増加に伴なって、透析技術も多様化し、人工腎臓に対してもより高い性能が要求されるようになってきた。すなわち、オンライン濾過透析やプッシュ・プル濾過透析においては非常に高い水透過性が要求され、通常の血液透析においては、低分子物質の高い除去能と共に、β_2－ミクログロブリン等の分子量１０，０００以上の物質の高い除去能が要求されている。また、これまでは血液中の有用な蛋白質であるアルブミンの透過は極力押さえる方向であったが、透析患者に蓄積してくる有害物質がアルブミンに強く結合していることが判明し、適度のアルブミンを透過させる膜も要求され、この様な膜を用いた人工腎臓による症状の改善も多く報告されている。

【０００５】

しかしながら、これらの要求を全て満足するような人工腎臓はいまだ得られていない。例えば特公平５－５４３７３号公報に開示されるポリスルホン膜は人工腎臓として良好なものではあるが、上述の濾過透析に要求される透水性や血液透析での低分子物質の除去能が今一歩である。特開平４－３００６３６号公報に示されるポリスルホン膜は透水性は十分であるが、尿素物質、とりわけ、β_2－ミクログロブリン等の分子量が大きい物質の除去能が今一歩である。さらに得られた中空糸膜を人工腎臓として製造する場合、透水性を保持するために付与する湿潤保持材（例えばグリセリン）の存在下でポッティングを行なう場合、中空糸同志の密着により、ポリウレタン等のポッティング材が、中空糸の間隙に浸透するのが困難でシール洩れを起すなどの生産上の大きな問題がある。

【０００６】

【発明が解決しようとする課題】

本発明は従来技術の問題点を解消し、水透過性が高く、尿毒物質の除去性能が高く、かつ、適度のアルブミン透過性がある人工腎臓を、中空糸紡糸時に得られた膜の良好な特性を保持して安定に、かつ容易に製造する方法を提供するものである。

【０００７】

【課題を解決するための手段】

本発明のポリスルホン系中空糸型人工腎臓の製造方法は、ポリスルホン系樹脂と親水性高分子を含む紡糸原液に、注入液として有機溶剤または有機溶剤と水との混合液を用いて紡糸された中空糸に、湿潤保持材を含浸し、湿潤保持材水溶液が付着した状態で、中空糸束を作成し、該中空糸束を人工腎臓用モジュールケースに挿入し、管板形成を行なって中間製品を作成後、湿潤保持材を水で洗浄し、その後滅菌処理する中空糸型人工腎臓の製造方法において、湿潤保持材を除去するための洗浄を５５℃以上の加熱水で行った後、水を

充填した状態で２０ＫＧｙ以上、３５ＫＧｙ以下の範囲の線量でガンマー線を照射し、親水性高分子を架橋して不溶化することを特徴とするポリスルホン系中空糸型人工腎臓の製造方法に関する。

【０００８】

また、アルブミンの透過率が０．３％以上、２．０％以下であり、かつ膜面積１．３ｍ^{2}のモジュールでのビタミンB^{12}のダイアリザンスが１４０以上であることを特徴とするポリスルホン系中空糸型人工腎臓に関する。

【０００９】

また、膜面積１．３ｍ^{2}のモジュールでの血液透析モードでの臨床使用におけるβ_2－ミクログロブリンの除去率が６０％以上であることを特徴とする上記(1)または(2)に記載のポリスルホン系中空糸型人工腎臓に関する。

【００１０】

また、膜面積１．３ｍ^{2}のモジュールでの血液透析モードでの臨床使用におけるβ_2－ミクログロブリンの除去率が７０％以上であることを特徴とする上記(1)または(2)に記載のポリスルホン系中空糸型人工腎臓に関する。

【００１１】

【発明の実施の形態】

詳細については後述する特定の紡糸原液、注入液を用いて、特定の乾式部の条件下で紡糸して得られる人工腎臓用として良好な特性を有する中空糸を用い、その特性を劣化させることなく保持して人工腎臓モジュールとする。そのために、中空糸に十分な量の湿潤保持材を付与してモジュールの組立て加工を行ない、湿潤保持材を除去した後は、水を充填した状態で製品とする。この際、中空糸に湿潤保持材を付与した状態で中空糸束を作成すると、中空糸同志が密着してポッティング材による管板形成が困難となるため、スペーサーを入れて密着を防止することはより好ましい方法である。

【００１２】

すなわち、中空糸に十分な量の湿潤保持材を付与した状態で中空糸束を作成し、管板形成を行なった後、湿潤保持材を水で洗浄し、しかるのち滅菌処理することを特徴とする方法で製造され、得られたポリスルホン系中空糸型人工腎臓は、アルブミンの透過率が３．０％以下であり、かつ膜面積１．３ｍ^{2}のモジュールでのビタミンB_{12}のダイアリザンスが１３５以上であることを特徴とするものである。

【００１３】

さらに、この製造方法においては、本願記載の好ましい条件を採用することにより、アルブミンの透過率が０．１％以上、２．４％以下であり、かつビタミンB_{12}のダイアリザンスが１３７以上であることを特徴とする人工腎臓が得られ、さらに好ましい条件の組合せでは、アルブミンの透過率が０．３％以上、２．０％以下であり、かつビタミンB_{12}のダイアリザンスが１４０以上であることを特徴とする人工腎臓が得られる。

【００１４】

また、本発明の製造方法において、好ましい製造条件を採用することにより、尿素のダイアリザンスが１９１以上の人工腎臓が得ることができ、より好ましい製造条件を採用することにより、尿素のダイアリザンスが１９２以上の人工腎臓が得ることができ、さらに好ましい製造条件を採用することにより、尿素のダイアリザンスが１９３以上の人工腎臓が得ることができる。

【００１５】

また、本発明の方法によれば、中空糸の水の透過性が５００ｍｌ／ｈｒ・ｍｍＨｇ・ｍ^{2}以上の人工腎臓が得ることができ、より好ましい製造条件を採用することにより、中空糸の水の透過性が６００ｍｌ／ｈｒ・ｍｍＨｇ・ｍ^{2}以上の人工腎臓が得ることも可能である。本発明の方法で得られた最良の臨床評価結果が得られた中空糸膜の水の透過性は８００ｍｌ／ｈｒ・ｍｍＨｇ・ｍ^{2}以上であった。

【００１６】

血液透析で良好な症状改善を得るためには、アルブミンの透過率（ふるい分け係数を％で

表示）は０．６％以上が好ましく、その上限は蛋白質損失量の制限（４～６グラム／１回の治療）から、２．０～３．０％程度となる。すなわち、本発明の好ましい態様は、アルブミンの透過率が０．６％以上、２．０％以下であり、かつ尿素やクレアチンなどの低分子尿毒素成分や、β_2－ミクログロブリンなどの高分子尿毒素成分の除去性能が従来品にくらべてより高い人工腎臓を提供する。

【００１７】

さらに血液濾過や血液濾過透析では高い透水性と尿毒素成分の除去性能を有し、かつアルブミンの透過率は、治療方法によって異なるが、０．１％以上、１．０％程度以下が好ましい。本発明は、アルブミンの透過率が１．０％以下で、尿毒素成分の除去性能や透水性が従来品にくらべてより高い人工腎臓をも提供するものである。

【００１８】

なお、臨床評価におけるβ_2－ミクログロブリンの除去率とビタミンB_{12}のダイアリザンスとは正の相関があり、ビタミンB_{12}のダイアリザンスは膜の性能の最も良い指標といえる。

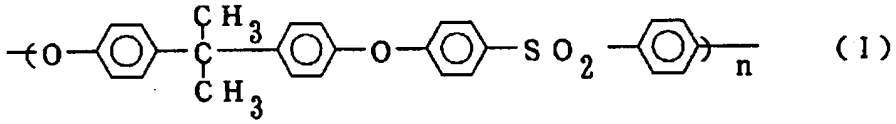
【００１９】

本発明のポリスルホン系中空糸型人工腎臓は、親水性高分子を含有するポリスルホン樹脂からなる中空糸膜で構成されている。

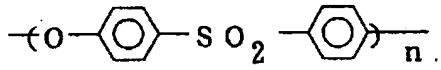
【００２０】

ポリスルホン樹脂としては、アモコ社やＢＡＳＦ社あるいはＩＣＩ社等から市販されている式（Ｉ）あるいは式（ＩＩ）で示されるものを例示することができる。

【化１】



（Ｉ）



（ＩＩ）

ただし、式中、ｎは正の整数を表わす。

【００２１】

特に、この中で式（Ｉ）で示される構造を有するアモコ社のＰ－３５００、またはその同等品が好ましい。しかし、原液粘度調整のため、Ｐ－１７００などを混合できることはいうまでもない。

【００２２】

また、親水性高分子とは、ポリビニルピロリドンもしくはポリエチレングリコールなどの親水性に優れた高分子であるが、特にポリビニルピロリドンが好ましい。ポリビニルピロリドンはＢＡＳＦ社、ＧＡＦ社等から市販されている、例えばＫ－３０やＫ－９０等の重量平均分子量３０，０００以上のものが好ましく使用される。

【００２３】

本発明の中空糸型人工腎臓を構成する中空糸膜は上述のポリスルホン樹脂と親水性高分子とを溶媒に溶解して得られる紡糸原液を中心部に注入液を吐出できる環状スリット口金から吐出し、いわゆる乾湿式紡糸法により紡糸される。

【００２４】

溶媒としては、ジメチルアセトアミド、ジメチルスルホキシド、Ｎ－メチルピロリドン、ジメチルホルムアミド等を単独もしくは混合して使用できる。その中でも、ジメチルアセトアミドは素材ポリマの分子量や孔径調節剤として少量添加する水との組合せにより、人工腎臓用として良好な特性の中空糸膜を得ることができ、好ましい溶媒である。

【００２５】

本発明の製造方法の紡糸原液におけるポリスルホン系樹脂の濃度は、好ましくは１４～２２重量％の範囲、より好ましくは１７～１９重量％の範囲である。

【００２６】

親水性高分子の濃度は、好ましくは５～１２重量％の範囲、より好ましくは７～１０重量％の範囲である。

【００２７】

特に人工腎臓として良好な特性の中空糸膜を、経済性を考慮し高速で紡糸して得るためには、紡糸原液の粘度が重要である。粘度が低い場合、乾式部における糸切れや中空糸の直径のばらつきが大きくなると共に、アルブミンの透過率の制御が困難となり好ましくない。また粘度が高い場合、中空糸の膜厚のばらつきが大きくなると共に尿毒素物質の除去能が低下し好ましくない。

【００２８】

本発明の製造方法の紡糸原液においては、溶媒としてジメチルアセトアミドを用いる場合、３０℃における粘度は２５～１３０ポイズの範囲（２０℃においては約３５～１７０ポイズ）が好ましく、４０～１１０ポイズの範囲がより好ましい。

【００２９】

この粘度の調節は紡糸原液中のポリスルホン樹脂の濃度、分子量、親水性高分子の濃度、分子量で行なうことができるが、最も好ましい方法は親水性高分子の分子量を変えることである。すなわち、例えば、重量平均分子量約４０，０００のポリビニルピロリドン（Ｋ－３０）と分子量約１，１００，０００のポリビニルピロリドン（Ｋ－９０）とを混合し、その混合比を変えることにより所望の粘度とする方法である。

【００３０】

具体的に好ましい例を示すと、ジメチルアセトアミドを溶媒として、アモコ社のポリスルホンＰ－３５００を濃度１８重量％とし、ポリビニルピロリドンの濃度を９重量％とする場合、Ｋ－３０とＫ－９０の混合比は、約９／０～５／４の範囲、より好ましくは約８／１～５．５／３．５の範囲となる。

【００３１】

また、本発明の紡糸原液においては、中空糸膜の孔径調節剤として少量の水を添加することが好ましい。最も好ましい溶媒であるジメチルアセトアミドを用いる場合、原液中に含まれる好ましい水の量ｙ（重量％）は、原液の粘度により規定され、次式

$$-0.01x+1.45 \leqq y \leqq -0.01x+2.25$$

を満足する範囲にある場合に良好な特性の中空糸膜を得ることができる。原液中に含まれる水の量ｙ（重量％）が次式

$$-0.01x+1.65 \leqq y \leqq -0.01x+2.05$$

を満足する範囲にある場合、より好ましい。ただし、ｘは紡糸原液の３０℃における粘度（ポイズ）であり、ｘは２５～１３０ポイズの範囲、好ましくは４０～１１０ポイズの範囲である。

【００３２】

水の添加が少ない場合は、紡糸原液の長期保管による白濁の生成（ポリスルホンオリゴマーが結晶化し白濁するとみられ、白濁が進むと紡糸中の糸切れの発生がみられるようになり好ましくない。）は押えられるが、細孔径が小さくなり、β_2－ミクログロブリン等の分子量が１０，０００以上の物質の除去能が低下し好ましくない。逆に水の添加が多い場合は、紡糸原液の安定性が不良となり、白濁化が起り、さらに、アルブミンの透過率が高くなりすぎ好ましくない。

【００３３】

さらに本発明の製造方法においては、口金の中心部から注入液を吐出し、中空糸の内表面をその凝固性により制御し、人工腎臓としての良好な特性を有する膜を得る。注入液としては、一般的に、中空糸の内表面から紡糸原液を緩慢に凝固させ、分離膜の緻密な活性層を形成させる目的で使用するため、凝固性が低いものが好ましく、アルコール等の有機溶剤単独、または水との混合液が使用可能である。

【００３４】
特に、本発明では、その回収のし易さや、高い性能を得るため、紡糸原液に使用する溶媒と水との混合溶液が好ましく、最も好ましい溶媒であるジメチルアセトアミドと水との混合溶媒がより好ましい。
【００３５】
このジメチルアセトアミドと水との混合溶媒を用いる場合、本発明の人工腎臓として良好な特性を有する膜を得るためには、注入液に含まれる水の量ｚ（重量％）が原液の粘度により規定され、次式
０．１４ｘ＋２５．５≦ｚ≦０．１４ｘ＋３７．５
を満足する範囲にあることが好ましい。注入液に含まれる水の量ｚ（重量％）が次式
０．１４ｘ＋２８．５≦ｚ≦０．１４ｘ＋３４．５
を満足する範囲にある場合、より好ましい。ただし、ｘは紡糸原液の３０℃における粘度（ポイズ）であり、ｘは２５～１３０ポイズの範囲、好ましくは４０～１１０ポイズの範囲である。
【００３６】
さらに、人工腎臓用の中空糸膜として、より良好な特性を有する膜は、原液中の水の量ｙ（重量％）と注入液中の水の量ｚ（重量％）との両者が上記のそれぞれの式を満足することによって得られる。
【００３７】
水の量が少ない場合には、紡糸原液の凝固が遅く内表面からの凝固が遅いため、乾式部での糸切れが起りやすく、また、アルブミン等の蛋白質の透過性が高くなりすぎる傾向もみられる。逆に水の量が多い場合には、β_2－ミクログロブリン等の分子量が大きい物質の除去性能が低下し、さらに水の量が多くなると低分子物質の除去性能も低下し好ましくない。
【００３８】
本発明の中空糸膜は上述のように設定された紡糸原液と注入液を用い、環状スリット型口金から直接凝固浴に導く湿式紡糸法、または口金からの中空糸を一旦気相中にさらした後、凝固浴中に導く乾湿式紡糸法で紡糸される。この際、良好な性能を得るためには、気相中（乾式部）に好ましくは０．１～１．０秒、より好ましくは０．２～０．８秒の範囲で走糸させる乾湿式紡糸法が好ましい。
【００３９】
乾式部の条件としては、相対湿度４０％以上が必要であり、好ましくは加湿した相対湿度７０％以上の湿潤気流中に接触させ、より好ましくは相対湿度８０％以上の湿潤気流中に接触させることにより良好な性能を得ることができる。
【００４０】
次に、このようにして口金から紡出された中空糸状の原液は凝固浴に導かれる。凝固浴では、溶媒とは混和するが、ポリスルホン樹脂に対しては凝固能を有する非溶媒である凝固液と接触し、外表面側からの支持層としての粗大孔スポンジ状構造の膜形成を行なう。
【００４１】
凝固液としては、非溶媒単独または２種以上を混合して用いることができるが、溶媒の回収の面から、紡糸原液の溶媒と水との混合溶液が好ましい。
【００４２】
凝固浴を出た中空糸は、水によって洗浄し、大部分の溶媒成分を除去した後、湿潤保持材溶液中に浸漬し、所定の長さに切断、所定の糸本数に集束して、中空糸内部の注入液が上記浸漬時に置換された湿潤保持材溶液を脱液し中空糸束を作成する。
【００４３】
湿潤保持剤としては、グリセリン、エチレングリコール、ポリプロピレングリコール、ポリエチレングリコール等の中空糸束を空気中に放置した場合にも、乾燥を防止できるアルコール類や無機塩の水溶液が使用できるが、特にグリセリンが好ましい。
【００４４】

グリセリンの場合には、乾燥による透過性の劣化を防止するためには、好ましくは５０重量％以上、より好ましくは６０～７５重量％、さらに好ましくは６５～７２重量％のグリセリン水溶液が用いられる。

【００４５】

湿潤保持剤水溶液の付着量は、中空糸膜の細孔中に該水溶液が存在する量を測定して抱液率として示す。この抱液率は膜の細孔容積率（空孔率）に容易に換算でき、膜の透析性能は一般に抱液率が高いものほど高くなる。本発明においては、製造工程中において乾燥による空孔率の低下を抑制するため、高い抱液率を保持した状態で製造して、中空糸膜の抱液率が従来のポリスルホン膜に比べ非常に高い、すなわち尿素やビタミンB_{12}等のダイアリザンスが高い人工腎臓を提供するものである。

【００４６】

すなわち、中空糸束を人工腎臓用モジュールケースに挿入する工程途中、あるいは製品の中空糸膜の抱液率が３５０～５００％の範囲、好ましくは３７０～４６０％の範囲、さらに好ましくは３９０～４４０％の範囲である。

【００４７】

なお、この抱液率は、製品の場合、水が充填されている場合が多いが、測定途中の乾燥による誤差をなくすため、６８重量％のグリセリン水溶液（比重１．１８）に置換して測定され、抱液率もその重量から算出される。すなわち、中空糸の内側に封入されているグリセリン水溶液を遠心分離器中で１５００ｒｐｍの回転で２０分間脱液し、６０～９０ｇ程の中空糸束を切出し、６８重量％のグリセリン水溶液が付着した中空糸束の重量Ａと、その中空糸束を水で洗浄してグリセリンを除去した後、１１０℃で乾燥した中空糸のみの重量Ｂを測定し、次式で算出された値である。

抱液率＝（Ａ－Ｂ）／Ｂ×１００（％）

なお、中空糸の周りにスペーサーを導入している場合は、そのスペーサーの重量を除いて、重量Ａ，重量Ｂの測定を行う。

【００４８】

これら湿潤保持材を付与することにより、人工腎臓として組立て加工する際の膜性能の低下を防止できるが、逆に、中空糸同志の密着が起こり、ポリウレタン等のポッティング材による管板形成の際、中空糸の間隙に浸透することが非常に困難となり、シール洩れを起こし、血液側と透析液側との管板による分離ができないという問題が生じる。この解決法としては、中空糸束を人工腎臓用ケースに挿入した後、低湿度の雰囲気中に長期間保管する方法（例えば、相対湿度４０％の室内に３日間程度以上保管）、非常に低湿度の気流をケースの両端部付近に当てた後さらに中空糸束の両端面に垂直方向の強い気流を当てて、糸束端部をばらけるようにする方法（例えば、相対湿度１０％以下の４０～６０℃の空気を約２時間、ケースの両端部付近に当てた後、垂直方向から空気を強く吹き付けて両端部の中空糸をばらけさせる）などを行なった後、管板形成を行なう方法などがあるが、より好ましい方法は湿潤保持材を付与した後、中空糸束を作成する以前の過程で中空糸同志の密着を防止するためのスペーサーを導入する方法である。

【００４９】

このスペーサーの導入法は人工腎臓として使用する際、透析液が中空糸束の中央（中心）部にまでよく流れ込み、透析性能を高める効果もある一石二鳥の効果がある。このスペーサーの導入は、中空糸１本又は２本の周囲にポリエステル、ポリアミド、ポリアクリロニトリル、セルロースアセテート、絹、綿などの線状物を中空糸に沿うように付加したり、螺旋状に巻回する方法で行なうことができる。

【００５０】

ただし、この方法でシール洩れを完全に防止するためには、直径が中空糸外径の約２分の１程度以上（約１２０ミクロン以上）の太い線状物を使う必要があり、人工腎臓のケースの径が大きくなりあまり好ましい方法ではない。より好ましい方法は次に述べる２段階にスペーサーを導入する方法である。すなわち、１段階目に中空糸１本又は２本の周囲にポリエステル等の線状物を中空糸に沿うように付加する方法、線状物を螺旋状に巻回する方

法のいずれかにより単位中空繊維素子を作り、さらに該単位中空繊維素子４本以上を集合させた周囲に２段階目のスペーサーとしての線状物を螺旋状に巻回して中空繊維束を作り、該中空繊維束５束以上を集合して、人工腎臓用の所定の中空糸本数となる中空糸束とする方法である。なお、この場合、単位中空繊維素子の作成は螺旋状に巻回する方法がより好ましい方法である。

【００５１】

この第１、第２段階に導入する線状物は、比較的嵩高性があり、かつ伸縮性がある捲縮繊維、加工糸、紡績糸などが好ましく用いられる。また、その太さはポリスルホン中空糸より細く、中空糸外径の２０分の１程度までであり、中空糸外径の２分の１から１０分の１程度が好ましい。

【００５２】

このスペーサーの導入を行なうことによって、膜の性能の乾燥による劣化を防止できる濃度（量）の湿潤保持材を付与した状態で管板形成が容易となり、これにより本発明の高い水透過性、高い尿毒素物質の除去能を有し、アルブミンの透過率が３％以下に制御された人工腎臓が高い工程収率で得られる。

【００５３】

このようにして得られた中空糸束の人工腎臓への組立て（モジュール化）は通常の方法で行なう。

【００５４】

すなわち、ポリスチレン樹脂等のケースに糸束を挿入し、ポリウレタン等のポッティング材を用い、遠心力を応用してケースの両端部に管板形成を行ない、リークテストを行なって人工腎臓用の形状とする。

【００５５】

次に、中空糸膜内部に残存する微量の溶媒や湿潤保持材などを水洗して除去し、水を充填した状態で滅菌し、製品である人工腎臓とする。この水洗は室温付近の水で行なうこともできるが、５５℃で２時間程度、８０℃で１５分程度の時間を要するため、５５℃以上の加熱水による洗浄が好ましい。また、短時間の洗浄を行なった後、５０℃以上の保温を行ない、その後短時間の洗浄を行なうなどの繰り返し洗浄も可能である。

【００５６】

滅菌は通常の方法、すなわち、９０℃以上の熱水を用いての滅菌や、ガンマー線（γ線）や電子線を用いる放射線による水を充填した状態での滅菌が適用できる。γ線や電子線を用いる放射線による滅菌は、膜中の親水性高分子の架橋による不溶化が起こる場合もあり好ましい方法である。本発明において親水性高分子として最も好ましいポリビニルピロリドンを使用した場合には、約２０ＫＧｙ～３５ＫＧｙの範囲の線量でγ線を照射すると、ポリビニルピロリドンの架橋による不溶化と同時に、医療器具としての滅菌も同時に行なうことができ、最も実用的な滅菌方法である。

【００５７】

この放射線滅菌によりポリビニルピロリドンの架橋による不溶化を同時に行なうことは、その溶出を押えることができ製品の安全性を高める。また、この方法により、ポリビニルピロリドンを製品の中空糸中に多く含有させることができ、そのため水との親和性が良好な膜となり、本願の高い性能を発現させることができる。なお、ポリビニルピロリドンの架橋による不溶化を行うために、滅菌に先立って別個に放射線照射する方法も可能であることはいうまでもないが、一度の放射線照射で架橋と滅菌を同時に行う方が、高性能の膜を得るために好ましい。

【００５８】

【実施例】

以下、実施例によって具体的に説明するが、本発明がこれによって限定されるものではない。また、本発明の特性の評価は次の方法により行なった。

【００５９】

［水透過性］

γ線滅菌を行なって完成した製品人工腎臓のケースを切断して得られる長さ約１５ｃｍの中空糸３０本を用いて、小型ガラス管モジュールを作成し、膜の外と内の圧力差、すなわち膜間圧力差を約１００ｍｍＨｇで水の透過量を測定し、ｍｌ／ｈｒ・ｍｍＨｇ・m^2で表わした。

【００６０】

[尿素およびビタミンB_{12}のダイアリザンス]

尿素６０ｇとビタミンB_{12}１．２ｇを水６０リットルに溶解し、血液側流量２００ｍｌ／ｍｉｎ、透析液側流量５００ｍｌ／ｍｉｎ、濾過速度を１０ｍｌ／ｍｉｎとして、透析器の血液側入口と出口、透析液側の入口と出口の濃度を測定し、血液側基準と透析液側基準のダイアリザンスをそれぞれ算出し、その平均値を用い、ｍｌ／ｍｉｎで表示した。

【００６１】

[アルブミンの透過率]

ヘマトクリット３０％、蛋白質濃度６ｇ／ｄｌ、３７℃の牛血２ｌをビーカーに入れ、血液側流量２００ｍｌ／ｍｉｎ、膜間圧力差を約１００ｍｍＨｇで１時間循環し、その間に得られる濾液はビーカーに戻す。その後、膜間圧力差を約６０ｍｍＨｇとして、１５分間隔に濾液３本を採取した。牛血を遠心分離して得られた血漿中のアルブミン濃度をＢＣＧ法（和光純薬）で、濾液中のアルブミン濃度をＣＢＢ法（東京化成）で測定し、３本の濾液の平均値からアルブミン透過率を算出した。

【００６２】

[β_2－ミクログロブリンの除去率]

体重５０ｋｇ～６０ｋｇで、かつ、透析前のβ_2－ミクログロブリンが２５～３５ｍｇ／ｌの６名の患者さんで、ヘパリンを抗凝固剤として、血液側流量２００ｍｌ／ｍｉｎ、透析液側流量５００ｍｌ／ｍｉｎ、４時間で除水量２．５～３．５ｌの血液透析を行ない、透析前後のβ_2－ミクログロブリン濃度をラテックス凝集免疫法で測定し、蛋白質濃度の補正を行ない算出し、平均値を用いる。

【００６３】

[紡糸原液粘度] Ｂ型粘度計（トキメック（株）ＤＶ－ＢII形ディジタル粘度計）を用い、容器内径の影響を受けないよう３００ｍｌ以上の紡糸原液を採取して測定した。

【００６４】

実施例１

ポリスルホン（アモコ社製“Ｐ－３５００”）１８部（以下単に「部」という場合は「重量部」を意味する）とポリビニルピロリドン（ＢＡＳＦ社製“Ｋ－３０”；分子量約４０，０００）６部とポリビニルピロリドン（ＢＡＳＦ社製“Ｋ－９０”；分子量約１，１００，０００）３部とを、ジメチルアセトアミド７１．９５部と水１．０５部との混合溶液に加えて、８０℃に保温しながら１２時間撹拌して溶解し、紡糸原液を調製した。この紡糸原液は３０℃で７６．９ポイズ（２０℃で１１３．１ポイズ）の均一で、わずかに乳白色を帯びた澄明液であった。

【００６５】

この紡糸原液を３０℃で環状スリット口金から吐出し、口金の中心部からジメチルアセトアミド６０部と水４０部とを混合して調製した注入液を注入した。乾式部分の長さを２５０ｍｍとし、その部分に相対湿度８８％の湿潤空気を流しながら紡糸速度４０ｍ／ｍｉｎで紡糸し、４０℃の凝固浴（ジメチルアセトアミド／水（重量比）＝２０／８０）に導き、凝固浴出の中空糸を洗浄後、６８重量％のグリセリンを含む水溶液に浸漬した。表面に付着した過剰のグリセリンを取り除いた後、中空糸２本の回りに５０デニール５フイラメント（約８８ミクロン）のポリエステル仮撚り加工糸を、中空糸１０ｍｍに対し０．５回の巻数でＺ方向に螺旋巻回して単位中空繊維素子とし、この単位中空繊維素子を２４単位集合し、その回りに同じポリエステル加工糸をほぼ同じピッチでＳ方向に螺旋巻回して２層にスペーサーを入れ、中空繊維束を作った。該中空繊維束を２２１束集合し、中空糸束を作成した。この中空糸束を遠心分離器中で回転させ中空糸内部の注入液と置換されて封入されているグリセリン水溶液を脱液し、人工腎臓用ケースに挿入するための中空糸束と

した。この中空糸の内径は２００ミクロン、外径２８０ミクロンであり、この中空糸束は中空糸１０，６０８本を集合したものであった。この中空糸束の抱液率は４２０％であった。

【００６６】

この中空糸束を内径４０ｍｍの人工腎臓用ケースに挿入し、両端部に仮のキャップをつけて、回転遠心力の場で、透析液側流入口からポリウレタンを流し込み、しかるのちポリウレタンを固化させた。次いで仮のキャップをはずし、ケースの両端部からはみだしているポリウレタンおよび中空糸束の端部近傍を切断し、ヘッダーキャップを取付け、０．８ｋｇ／ｃｍ^{2}の加圧空気を用いて漏洩試験を行なった。

【００６７】

１０００本のサンプルを用いて漏洩試験を行なった結果、１２本の不良品が発生していた。その原因を調査したところ、ケースに中空糸束を充填する際にケースの端部や内壁に接触したことによる単純作業ミスによる折れ糸、切れ糸に起因するものであり、ポリウレタン管板部のシール洩れは全くみられなかった。

【００６８】

次に、漏洩試験に合格したモジュールを８０℃で３０分間逆浸透膜を通した純水で洗浄し、包装した後、３２ＫＧｙのγ線を照射し滅菌し、有効長１９５ｍｍ、有効面積１．３ｍ^{2}の人工腎臓透析器を作成した。この透析器は透析型人工腎臓装置承認基準に全ての項目で合格するものであった。このモジュールから切出した中空糸の水透過性は８１５ｍｌ／ｈｒ・ｍｍＨｇ・ｍ^2、モジュールのアルブミンの透過率は１．２％、尿素のダイアリザンスは１９５ｍｌ／ｍｉｎ、ビタミンB_{12}のダイアリザンスは１４３ｍｌ／ｍｉｎであった。

【００６９】

また、このモジュールを使用して臨床評価した際のβ_2－ミクログロブリンの除去率は７３％と非常に高い結果であり、残血等の使用上特に問題となる点はみられなかった。なお、このモジュールから切出した中空糸束の抱液率は４２０％であった。

【００７０】

実施例２

ポリスルホン（アモコ社製“Ｐ－３５００”）１８部とポリビニルピロリドン（ＢＡＳＦ社製“Ｋ－３０”）９部とを、ジメチルアセトアミド７１．６部と水１．４０部との混合溶液に加えて、９０℃に保温しながら１２時間撹拌して溶解し、紡糸原液を調製した。この紡糸原液は３０℃で２８．４ポイズ（２０℃で３８．８ポイズ）であった。

【００７１】

この紡糸原液を３０℃で環状スリット口金から吐出し、口金の中心部からジメチルアセトアミド６５部と水３５部とを混合して調製した注入液を注入した。乾式部分の長さを３５０ｍｍとし、その部分で相対湿度８４％の湿潤空気に当てながら紡糸速度４０ｍ／ｍｉｎで紡糸し、以下部分を除き実施例１と同様の方法で人工腎臓透析器を作成した。この途中で１０００本のサンプルを用いて漏洩試験を行なった結果、１７本の不良品が発生したが、その原因は実施例１と同じであった。なお、この中空糸束の抱液率は３８０％であった。

【００７２】

このようにして得られた有効面積１．３ｍ^{2}の透析器は透析型人工腎臓装置承認基準に全ての項目で合格した。この透析器から切出した中空糸の水透過性は７１０ｍｌ／ｈｒ・ｍｍＨｇ・ｍ^{2}であり、モジュールのアルブミン透過率は０．４％、尿素およびビタミンB_{12}のダイアリザンスはそれぞれ１９４ｍｌ／ｍｉｎ、１３９ｍｌ／ｍｉｎであった。また、このモジュールを使用して臨床評価を行なった際のβ_2－ミクログロブリンの除去率は６７％であり、残血等の使用上特に問題となる点はみられなかった。なお、このモジュールから切出した中空糸束の抱液率は３８０％であった。

【００７３】

実施例３

ポリスルホン（アモコ社製“Ｐ－３５００”）１８部とポリビニルピロリドン（ＢＡＳＦ社製“Ｋ－３０”）９部とを，ジメチルアセトアミド７１．８部と水１．２部との混合溶液に加えて、８０℃に保温しながら１２時間撹拌して溶解し、紡糸原液を調製した。この紡糸原液は３０℃で２６．８ポイズであった。以下、注入液組成をジメチルアセトアミド６０部と水４０部と混合した注入液を用いた以外は実施例１と同様の方法で人工腎臓透析器を作成した。なお、ここで用いた中空糸束の抱液率は３５０％であった。

【００７４】

この透析器から切出した中空糸の水透過性は７４０ｍｌ／ｈｒ・ｍｍＨｇ・m^2であり、モジュールのアルブミン透過率は０．１％、尿素およびビタミンB_{12}のダイアリザンスはそれぞれ１９２ｍｌ／ｍｉｎ、１３６ｍｌ／ｍｉｎであった。また、このモジュールを使用して臨床評価を行なった際のβ_2－ミクログロブリンの除去率は６２％であり、残血等の使用上特に問題となる点はみられなかった。なお、この透析器の中空糸の抱液率は３６０％であった。

【００７５】

実施例４

実施例１の途中段階の中空繊維束をそれぞれ１７０束および３０６束集合して中空糸束を作成し、そのそれぞれを内径３５．５ｍｍおよび４６．５ｍｍの人工腎臓用ケースに挿入し、実施例１と同じ方法で人工腎臓透析器を作製した。

【００７６】

それぞれの有効面積は１．０m^2と１．８m^2であり、ビタミンB_{12}のダイアリザンスを測定したところ１２７ｍｌ／ｍｉｎと１６５ｍｌ／ｍｉｎであった。

実施例５

実施例３の途中段階の中空糸束を用いて、集合本数を変えて中空糸束を作り、それぞれを内径３５．５ｍｍ、４４．０ｍｍおよび４６．５ｍｍの人工腎臓用ケースに挿入して、それぞれの有効面積が１．０m^2、１．６m^2および１．８m^2の人工腎臓透析器を実施例３と同様の方法で作成した。

【００７７】

尿素およびビタミンB_{12}のダイアリザンスならびにアルブミンの透過率を測定したところ、尿素のダイアリザンスはそれぞれ１８７ｍｌ／ｍｉｎ、１９５ｍｌ／ｍｉｎおよび１９７ｍｌ／ｍｉｎ、ビタミンB_{12}のダイアリザンスはそれぞれ１２２ｍｌ／ｍｉｎ、１４７ｍｌ／ｍｉｎおよび１５６ｍｌ／ｍｉｎ、アルブミンの透過率はそれぞれ０．２％、０．１％および０．２％であった。

【００７８】

実施例６

ポリスルホン（アモコ社製“Ｐ－３５００”）１８部とポリビニルピロリドン（ＢＡＳＦ社製“Ｋ－３０”）６部とポリビニルピロリドン（ＢＡＳＦ社製“Ｋ－９０”）３部とを、ジメチルアセトアミド７１．８５部と水１．１５部との混合溶液に加えて、９０℃に保温しながら１２時間撹拌して溶解し、紡糸原液を調製した。この紡糸原液は３０℃で７１．４ポイズであった。

【００７９】

この紡糸原液を４０℃で環状スリット口金から吐出し、口金の中心部からジメチルアセトアミド５８部と水４２部とを混合して調製した注入液を注入した。乾式部分の長さを３５０ｍｍとし、その部分に相対湿度８５％の湿潤空気を流しながら紡糸速度４２ｍ／ｍｉｎで４５℃の凝固浴に導き、以下実施例１と同様の方法で人工腎臓透析器を作製した。なお、途中段階の人工腎臓用ケースに挿入する時点での中空糸束の抱液率は４１０％であった。

【００８０】

このようにして得られた有効面積１．３m^2の透析器から切り出した中空糸の水透過性は８１０ｍｌ／ｈｒ・ｍｍＨｇ・m^2であり、アルブミン透過率は０．６％、尿素およびビタミンB_{12}のダイアリザンスはそれぞれ１９５ｍｌ／ｍｉｎ、１４２ｍｌ／ｍｉｎであっ

た。また、このモジュールを使用して臨床評価を行なった際のβ$_2$－ミクログロブリンの除去率は７４％であり、残血等の使用上特に問題となる点はみられなかった。なお、このモジュールの中空糸の抱液率は４２０％であった。

【００８１】

実施例７

実施例６の原液を用いて、ジメチルアセトアミド５６部と水４４部とを混合して調整した注入液を用いる以外は、実施例６と同様の方法で人工腎臓透析器を作製した。なお、途中段階の中空糸束の抱液率は４００％であった。

【００８２】

このようにして得られた有効面積１．３m^{2}の透析器から切り出した中空糸の水透過性は７６０ｍｌ／ｈｒ・ｍｍＨｇ・m^{2}であり、アルブミン透過率は０．２％、尿素およびビタミンB$_{12}$のダイアリザンスはそれぞれ１９４ｍｌ／ｍｉｎ、１４０ｍｌ／ｍｉｎであった。また、このモジュールを使用して臨床評価を行なった際のβ$_2$－ミクログロブリンの除去率は７１％であり、残血等の使用上特に問題となる点はみられなかった。なお、このモジュールの中空糸の抱液率は４１０％であった。

【００８３】

実施例８

ポリスルホン（アモコ社製“Ｐ－３５００”）１８部とポリビニルピロリドン（ＢＡＳＦ社製“Ｋ－３０”）７部とポリビニルピロリドン（ＢＡＳＦ社製“Ｋ－９０”）２部とを、ジメチルアセトアミド７１．８５部と水１．１５部との混合溶液に加えて、９０℃に保温しながら１２時間撹拌して溶解し、紡糸原液を調製した。この紡糸原液は３０℃で５３．０ポイズであった。

【００８４】

この紡糸原液を４０℃で環状スリット口金から吐出し、口金の中心部からジメチルアセトアミド６０部と水４０部とを混合して調製した注入液を注入し、以下実施例６と同様の方法で人工腎臓透析器を作製した。なお、途中段階の中空糸束の抱液率は３９０％であった。

【００８５】

このようにして得られた有効面積１．３m^{2}の透析器から切り出した中空糸の水透過性は６８０ｍｌ／ｈｒ・ｍｍＨｇ・m^{2}であり、アルブミン透過率は０．３％、尿素およびビタミンB$_{12}$のダイアリザンスはそれぞれ１９３ｍｌ／ｍｉｎ、１４０ｍｌ／ｍｉｎであった。

【００８６】

比較例１

ポリスルホン（アモコ社製“Ｐ－３５００”）１８部とポリビニルピロリドン（ＢＡＳＦ社製“Ｋ－３０”）９部とを、ジメチルアセトアミド４４部とジメチルスルホキシド２８部と水１．０部との混合溶液に加えて、８０℃に保温しながら１５時間撹拌して溶解し、紡糸原液を調製した。この紡糸原液は３０℃で３２．９ポイズであった。この紡糸原液を３０℃で環状スリット口金から吐出し、口金の中心部からジメチルアセトアミド６０部と水４０部とを混合した注入液を注入した。以下、実施例１と同様の方法で人工腎臓透析器を作成した。

【００８７】

この透析器から切出した中空糸の水透過性は８３０ｍｌ／ｈｒ・ｍｍＨｇ・m^{2}であり、モジュールのアルブミン透過率は０．２％、ビタミンB$_{12}$のダイアリザンスは１３２ｍｌ／ｍｉｎであった。また、このモジュールを使用して臨床評価を行なった際のβ$_2$－ミクログロブリンの除去率は４９％と低い値であった。なお、この透析器の中空糸の抱液率は３４０％であった。

【００８８】

比較例２

実施例１の凝固浴出の中空糸を洗浄後、４５重量％のグリセリンを含む水溶液に浸漬した

。表面に付着した過剰のグリセリンを取り除いた後、一辺が３０ｃｍの６角形のかせに巻取り、室温で通風乾燥した後、かせから切出して中空糸束を作製した。この中空糸束の抱液率は２７０％であった。この中空糸束は中空糸１０，６０８本を集合したものである。中空糸束を内径４０ｍｍの人工腎臓用ケースに挿入し、中空糸束の両端面に垂直方向の乾燥空気を当てて糸束端部をばらけさせた後、実施例１と同様の方法で管板形成を行ない、透析液側から加圧空気を入れ、血液側に水を満たしてのバブルポイント法による漏洩試験を行なった後、実施例１と同様の方法でγ線滅菌を行なって人工腎臓透析器を作製した。

【００８９】

このモジュールから切出した中空糸の水透過性は４１０ｍｌ／ｈｒ・ｍｍＨｇ・m^2、アルブミン透過率は０．３％、尿素のダイアリザンスは１９０ｍｌ／ｍｉｎ、ビタミンB_{12}のダイアリザンスは１２５ｍｌ／ｍｉｎと低い値となった。すなわち、低濃度のグリセリン付加の場合にはスペーサーなしでの管板形成が容易であるが、乾燥による中空糸の透過性の劣化が起り、本発明のような高い性能の人工腎臓の製造は困難であった。なお、この透析器の中空糸の抱液率は３００％であった。

【００９０】

【発明の効果】

本発明によれば、水透過性が高く、尿毒物質の除去性能が高く、かつ適度のアルブミン透過性がある人工腎臓を、中空糸紡糸時に得られた膜の良好な特性を保持して安定に、かつ容易に製造することができる。

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審査官 稲村 正義

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